

REMARKS

The Office Action of March 9, 2009, has been received and reviewed. The claims are to be amended as previously set forth. All amendments and claim cancellations are made without prejudice or disclaimer. No new matter has been presented. Reconsideration is respectfully requested.

Claim Objections

Claims 1 and 31 stand objected to for various informalities. Applicants note that the objection to claim 31 is moot as claim 31 is cancelled herein. Claim 1 stands objected to as the phrase “JAK-binding site” is missing an article (e.g., “a JAK-binding site”). Applicants note that appropriate correction has been made in the foregoing amendments to the claims.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 31 stands rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite. Applicants note that the rejection of claim 31 is moot as claim 31 is cancelled herein.

Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claim 31 stands rejected under 35 U.S.C. § 112, first paragraph, as assertedly failing to comply with the enablement requirement. Applicants note that the rejection of claim 31 is moot as claim 31 is cancelled herein.

Rejection under 35 U.S.C. § 112, First Paragraph, Written Description

Claim 31 stands rejected under 35 U.S.C. § 112, first paragraph, as assertedly failing to comply with the written description requirement. Applicants note that the rejection of claim 31 is moot as claim 31 is cancelled herein.

Rejections under 35 U.S.C. §§ 102(b) and 103(a)

Claims 1, 3, 11, 13, 16, and 31 stand rejected under 35 U.S.C. § 102(b) and/or 35 U.S.C. § 103(a) as assertedly anticipated and/or obvious over Eyckerman et al. (1999 Eur. Cytokine Netw. 10(4):549-556) (hereinafter “Eyckerman”). Specifically, it was asserted that Eyckerman

taught recombinant receptors comprising the mouse leptin receptor with at least one mutation in the cytoplasmic domain and a heterologous myc-tag. Final Office Action of November 10, 2008, at page 4. It was further asserted that the receptor of Eyckerman meets all the structural requirements of the claims, but does not meet the functional element of “wherein the activation of said recombinant receptor is inhibited by binding of a fusion protein to said heterologous bait polypeptide, said fusion protein comprising a prey polypeptide and at least one of an inhibitor of the activation of said recombinant receptor that is selected from the group consisting of a member of the SOCS family, a JAK-phosphatase, and a STAT-phosphatase.” *Id.* at page 4. However, the Examiner asserts that where the products seem identical except for the functional element, the burden shifts to the applicant. *Id.* Applicants note that the rejection of claim 31 is moot as claim 31 is cancelled herein. Applicants respectfully traverse the remaining rejections as hereinafter set forth.

Unless a single prior art reference describes “all of the limitations claimed” and “all of the limitations [are] arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102.” *Net MoneyIN Inc. v. VeriSign Inc.*, No. 07-1565, slip op. at 17-18 (Fed. Cir. Oct. 20, 2008). A single prior art reference must “clearly and unequivocally” describe the claimed invention “without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.” *Id.* at 19 (citing *In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972)). Applicants respectfully assert that claims 1, 3, 11, 13, and 16 cannot be anticipated or rendered obvious by Eyckerman as Eyckerman does not describe “all of the limitations claimed.” For example, Eyckerman does not describe a bait polypeptide.

The Examiner asserts, at page 4 of the Office Action of March 9, 2009, that the myc-tag present on the recombinant receptors of Eyckerman is equivalent to a heterologous bait polypeptide. In support of this position, the Examiner cites Fujiwara et al. (2002), Hilpert et al (2001), Estojak et al (1995), Bao et al. (1996), Bannasch et al (1999) and Junqueira et al. (2003). Applicants respectfully disagree.

Applicants submit that the terms “bait” and “tag” are clearly different for the person ordinarily skilled in the art as used in the application. A “tag” is a short peptide that can be used

for the identification or isolation of a protein. A “bait” is a polypeptide that is used to fish a prey out of a mixture of candidate interacting molecules. This difference is clearly recognized in the art, and is illustrated by, but certainly not limited to, the article by Van Crielinge (1999; arguments regarding which were provided in the response filed October 23, 2008 and are herein incorporated by this reference). Multiple other articles, such as Hertveld et al (2003; provided in the IDS submitted herewith), where the authors mention “tagged baits” support this interpretation, indicating the different functions – and meaning – of the terms tag and bait. Especially in the field of TapTag technology, where protein complexes are immunoprecipitated, there is extensive evidence for the different meaning of both terms. It is important to stress that tags are chosen in such a way that they do not interfere with the bait action and will not act as a bait, as otherwise the combination of bait and tag would give rise to false positives.

Applicants note that Eyckerman cannot anticipate or render obvious the claims as Eyckerman does not teach or suggest all the elements claimed. Specifically, Eyckerman does not teach or suggest “wherein the activation of said recombinant receptor is inhibited by binding of a fusion protein to said heterologous bait polypeptide, said fusion protein comprising a prey polypeptide and at least one of an inhibitor of the activation of said recombinant receptor that is selected from the group consisting of a member of the SOCS family, a JAK-phosphatase, and a STAT-phosphatase.”

The Examiner, at pages 7-8 of the Office Action of November 10, 2008, asserts that, as far as the Examiner can determine, the mutant receptor described by Eyckerman would be inhibited if contacted with a fusion polypeptide such as those described in the instant application (e.g., one comprising both a polypeptide that binds to myc and another one that comprises an inhibitor).” The Examiner further argues that Fujiwara et al. (2002) uses the myc tag as a bait. However, based on the results of Fujiwara, a person of ordinary skill in the art would conclude that the myc tag is indeed NOT suitable as bait (e.g., that a prey polypeptide which binds to myc and contains an activation site inhibitor would NOT be capable of inhibiting the claimed receptors). Indeed, the results obtained by Fujiwara with a single myc tag and the monoclonal antibody 9E10 (which is the standard antibody for detection of the Myc tag) are negative (Fujiwara at p. 12733: “Under the same conditions using a single MYC tag as bait, growth of yeast transformed with the 9E10 ScFv prey plasmid could hardly be detected”). Only in the case

of antibody 3DX, obtained after four rounds of mutagenesis, could some activity could be detected with a single myc tag. However, this activity is far below the level of the positive control and in the range of the background signal (Figure 3B of Fujiwara et al.).

Moreover, even if one would consider the myc tag, used in the construct of Eyckerman et al. as a bait, it is clear from those results of Fujiwara et al. that the receptor taught by Eyckerman cannot fulfill the functional limitation of being activateSd by binding of a ligand and a prey polypeptide. Indeed, even if one would assume that a fusion of the 3DX antibody with an activation domain would bind with the same affinity as the antibody alone, the signal would be far below the normal signal of a positive control, and within the background level of the non-activated receptor. Consequently one of ordinary skill in the art would conclude that the myc tag of the Eyckerman construct would not allow the “recombinant receptor [to be] inhibited by binding of a fusion protein to said heterologous bait polypeptide” as recited by claim 1.

In addition, the myc tag as used and understood by the person of ordinary skill in the art is a peptide of 11 AA (sequence EEQKLISEEDL – as present in pGBKT7 cited by Fujiwara et al. – or EEQKLISDEEL). The fact that these are the myc tags found in practical use is recognized in Hilpert et al, 2001, cited by the examiner (p2 as printed) The publications of Estojak et al (1995), Bao et al. (1996), Bannasch et al (1999) and Junqueira et al. (2003) use far larger fragments (at least 176 AA) as baits, and therefore, those baits are not covered by the definition of myc tag, as used by the person skilled in the art. Accordingly, one of ordinary skill in the art would conclude that the myc tag alone is not the bait used in Estojak et al (1995), Bao et al. (1996), Bannasch et al (1999) and Junqueira et al. (2003).

Further, Eyckerman does not disclose a prey/inhibitor fusion polypeptide as described in the instant specification. The prey, coupled to an inhibitor, is an essential element of the invention, as expressed in the claims. A person of ordinary skill in the art would not find such a prey fusion construct described or enabled in the teachings of Eyckerman. Further, one of ordinary skill in the art would have no knowledge (or motivation) that such a prey fusion construct could be used to inhibit the receptor. Additionally, even using the disclosure of the present application, it is unlikely that the Eyckerman receptor could be inhibited without burdensome experimentation in creating the anti-myc/inhibitor fusion necessary for myc-tagged protein of Eyckerman to be inhibited as claimed. Thus, no reasonable expectation of success

exists in modifying the teachings of Eyckerman to arrive at the present claims.

The myc-tag is a short peptide of 10 amino acids that can be bound by an antibody, but is generally incapable of binding to a normal protein by the classical protein-protein interaction normally associated with cellular function; although the tag is extensively used in the art, there are no protein-protein interactions described with the myc-tag other than with myc-binding antibodies. Thus, inhibition of the myc-tagged protein of Eyckerman would only work through the cytoplasmic expression of a functional myc-binding antibody, fused to an inhibitor. It would have been clear to one of ordinary skill in the art that this would not work with classical heavy/light chain antibody complexes, as these are not found in the cytoplasm. If one of skill in the art attempted to develop a single chain antibody fused to an activation domain, such development would not yield predictable results, as the exact folding and requisite S-S bridge formation would be unpredictable for such a molecule without extensive experimentation. Moreover, even if one could obtain such a construct, it is unsure whether the inhibitor, fused to such a single chain antibody, could inhibit the recombinant receptor in coordination while the anti-myc portion is bound to the myc-tag. Compared with bait/prey interactions, the anti-myc antibody interaction would be a bulky complex where steric hindrance would be expected to prevent inhibition of the receptor. Thus, applicants respectfully submit that the receptors of Eyckerman cannot be inherently capable of being inhibited when contacted with an anti-myc/inhibitor fusion as the requisite anti-myc polypeptides have not been developed for intracellular use and there is no reasonable expectation of the successful function even if developed.

Consequently, one of ordinary skill in the art would conclude that Eyckerman does not teach or suggest each and every element of claims 1, 3, 11, 13, and 16 (i.e. a bait polypeptide).

In view of at least the foregoing, applicants respectfully request the withdrawal of the rejections of claims 1, 3, 11, 13, and 16 under 35 U.S.C. §§ 102(b) and 103(a) and reconsideration of same.

CONCLUSION

In light of the above amendments and remarks, applicants respectfully request reconsideration of the application. If questions remain after consideration of the foregoing, or if

the Office should determine that there are additional issues which might be resolved by a telephone conference, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Daniel J. Morath', with a long horizontal flourish extending to the right.

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